



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US97/19153 (22) International Filing Date: 17 October 1997 (17.10.97) (30) Priority Data: 08/735,052 22 October 1996 (22.10.96) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventor: SINGER, Robert, Ernest, Jr.; 8700 Ma- son-Montgomery Road, Mason, OH 45040 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).		(81) Designated States: AU, BR, CA, CN, KR, MX, NZ, SG, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: ORAL COMPOSITIONS CONTAINING ZINC CITRATE SALTS (57) Abstract Oral compositions containing an alkali metal or ammonium zinc citrate to provide protection against colds and flu.		

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ORAL COMPOSITIONS CONTAINING ZINC CITRATE SALTS

5

TECHNICAL FIELD

The present invention relates to a method of preventing or controlling colds and similar maladies, such as flu, through the use of an oral composition containing an alkali metal or ammonium zinc citrate applied to the gingival or oral mucosal tissue of the subject susceptible to colds.

BACKGROUND OF THE INVENTION

The common cold, although not usually a serious illness, is a highly prevalent, discomforting and annoying affliction. The term "common cold" is applied to minor respiratory illnesses caused by a variety of different respiratory viruses. While rhinoviruses are the major known cause of common colds, accounting for approximately 30 percent of colds in adults, viruses in several other groups are also important. While immune responses occur, and infection with some respiratory tract viruses therefore could be prevented by a vaccine, development of a polytypic vaccine to cover all possible agents is impractical. Thus, the problem of controlling acute upper respiratory disease presents complex challenges, and the long-desired discovery of a single cure for the common cold is an unrealistic expectation.

With rhinovirus infection, symptoms of nasal discharge, nasal congestion, and sneezing usually commence on the first day of illness and progress to maximum severity by the second or third day. The costs of treating colds with over-the-counter medications in the United States is estimated at an annual cost of over 1.5 billion dollars. The direct costs of treatment in outpatient clinics is estimated at almost four billion dollars. Indirect costs, based on the amount of loss in wages because of restricted activity are substantially higher.

At present, only symptomatic treatment is available for the common cold; the majority of these drugs are taken orally. Exemplary prior art oral compositions for treatment of nasal and other cold, flu, allergy and sinus symptoms and the discomfort, pain, fever and general malaise associated therewith generally contain an analgesic (aspirin or acetaminophen) and one or more antihistamines, decongestants, cough suppressants, antitussives and expectorants. Other specific pharmaceutical actives for nasal symptoms (e.g., congestion) generally contain either oxymetazoline or phenylephrine. These actives are generally delivered topically to the nasal mucosa via a nasal spray. For individuals with certain medical conditions such as heart disease, hypertension, diabetes or thyroid disorders, oral

drugs such as decongestants could pose a risk of unfavorable drug interactions and may cause an adverse reaction. It would, therefore, be highly desirable to deliver relief from specific nasal symptoms via compositions without the need for such pharmaceutical actives.

5 It has been discovered that topical application of an alkali metal or ammonium zinc citrate to the gingival or oral mucosal tissues of a subject susceptible to colds and/or flu helps to reduce the incidence of such maladies.

It is therefore an object of the present invention to provide topical oral compositions which provide treatment to prevent colds and flu.

10 SUMMARY OF THE INVENTION

The present invention relates to a method of reducing colds and cold-like symptoms, such as flu, in subjects susceptible to such maladies by applying a composition containing an effective amount of an alkali metal or ammonium zinc citrate to the gingival or oral mucosal tissues.

15 DETAILED DESCRIPTION OF INVENTION

The compositions of the present invention contain certain essential components as well as non-essential components.

Alkali Metal or Ammonium Zinc Citrate

20 The zinc salts found useful in the compositions used in the present method are described in U.S. Patents 4,289,754, September 15, 1981, and 4,325,939, April 20, 1982, both incorporated herein by reference in their entirety.

The preferred compound is sodium zinc citrate.

25 The amount of the zinc compounds used in the composition used in the method described herein are from about 0.1% to about 11%, preferably from about 0.1% to about 5%.

Acceptable Carrier

30 The carrier for the active component(s) can be any vehicle suitable for use in the oral cavity. Such carriers include the usual components of mouthwashes, toothpastes, tooth powders, prophylaxis pastes, lozenges, gums and the like and are more fully described hereinafter. Dentifrices and mouthwashes are the preferred systems.

35 In addition to the active agent(s), the present compositions may contain antiplaque/gingivitis agent such as quaternary ammonium compounds, water insoluble agents such as triclosan, teas, as defined herein later, and stannous salts. These types of agents are described in U.S. patent 4,894,220; January 16, 1990 to Nabi et al, U.S. Patent 4,656,031, April 7, 1987 to Lane et al; and U.S. Patent 5,004,597, April 2, 1991 to Majeti et al. All incorporated herein by reference in

their entirety.

The abrasive polishing material contemplated for use in the present invention can be any material which does not excessively abrade dentin. These include, for example, silicas including gels and precipitates, calcium carbonate, dicalcium orthophosphate dihydrate, calcium pyrophosphate, tricalcium phosphate, calcium polymetaphosphate, insoluble sodium polymetaphosphate, hydrated alumina, and resinous abrasive materials such as particulate condensation products of urea and formaldehyde, and other such as disclosed by Cooley et al. in U.S. Patent 3,070,510, December 25, 1962, incorporated herein by reference. Mixtures of abrasives may also be used.

Silica dental abrasives, of various types, can provide the unique benefits of exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentin. Silica abrasive materials are also exceptionally compatible with sources of soluble fluoride and polyphosphonates. For these reasons they are preferred for use herein.

The silica abrasive polishing materials useful herein, as well as the other abrasives, generally have an average particle size ranging between about 0.1 to 30 microns, preferably 5 and 15 microns. The silica abrasive can be precipitated silica or silica gels such as the silica xerogels described in Pader et al., U.S. Patent No. 3,538,230, issued March 2, 1970 and DiGiulio, U.S. Patent No. 3,862,307, June 21, 1975, both incorporated herein by reference. Preferred are the silica xerogels marketed under the tradename "Syloid" by the W. R. Grace & Company, Davison Chemical Division. Preferred precipitated silica materials include those marketed by the J. M. Huber Corporation under the tradename, "Zeodent", particularly the silica carrying the designation "Zeodent 119". These silica abrasives are described in U.S. Patent No. 4,340,583, July 29, 1982, incorporated herein by reference.

The abrasive in the compositions described herein is present at a level of from about 6% to about 70%, preferably from about 15% to about 25% when the dentifrice is a toothpaste. Higher levels, as high as 90%, may be used if the composition is a toothpowder.

The compositions of the present invention may also contain a soluble fluoride ion source such as sodium, potassium or lithium fluorides, stannous fluoride, and sodium monofluorophosphate among many others. The fluoride source should be sufficient to provide from about 50 to about 3500 ppm fluoride.

Flavoring agents can also be added to dentifrice compositions. Suitable flavoring agents include, among many others, oil of wintergreen, oil of peppermint, oil of spearmint, and oil of clove. Sweetening agents which can be used include

aspartame, acesulfame, saccharin, dextrose, levulose and sodium cyclamate. Flavoring and sweetening agents are generally used in dentifrices at levels of from about 0.005% to about 2% by weight.

Dentifrice compositions can also contain emulsifying agents. Suitable
5 emulsifying agents are those which are reasonably stable and foam throughout a wide pH range, including nonsoap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents. Many of these suitable surfactants are disclosed by Gieske et al. in U.S. Patent No. 4,051,234, September 27, 1977, incorporated herein in its entirety by reference.

10 Water is also present in the toothpastes of this invention. Water employed in the preparation of commercially suitable toothpastes should preferably be deionized and free of organic impurities. Water generally comprises from about 10% to 50%, preferably from about 20% to 40%, by weight of the toothpaste compositions herein. These amounts of water include the free water which is added plus that which is
15 introduced with other materials such as with sorbitol.

In preparing toothpastes, it is necessary to add some thickening material to provide a desirable consistency. Preferred thickening agents are carboxyvinyl polymers of the type mentioned previously herein, xanthan gum, carrageenan, hydroxyethyl cellulose and water soluble salts of cellulose ethers such as sodium
20 carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Natural gums such as gum karaya, gum arabic, and gum tragacanth can also be used. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. Thickening agents in an amount from 0.5% to 5.0% by weight of the total composition can be used.

25 It is also desirable to include some humectant material in a toothpaste to keep it from hardening. Suitable humectants include glycerin, sorbitol, xylitol, and other edible polyhydric alcohols at a level of from about 5% to about 70%.

Another preferred embodiment of the present invention is a mouthwash composition. Conventional mouthwash composition components can comprise the
30 carrier for the active agents of the present invention. Mouthwashes generally comprise from about 20:1 to about 2:1 of a water/ethyl alcohol solution and preferably other ingredients such as flavor, sweeteners, humectants and sudsing agents such as those mentioned above for dentifrices. The humectants, such as glycerin and sorbitol give a moist feel to the mouth. Generally, on a weight basis
35 the mouthwashes of the invention comprise 0% to 60% (preferably 10% to 25%) ethyl alcohol, 0% to 20% (preferably 5% to 20%) of a humectant, 0% to 2% (preferably 0.01% to 0.15%) emulsifying agent, 0% to 0.5% (preferably 0.005% t

0.06%) sweetening agent such as saccharin, 0% to 0.3% (preferably 0.03% to 0.3%) flavoring agent, and the balance water.

Suitable lozenge and chewing gum components are disclosed in U.S. Patent No. 4,083,955, April 11, 1978 to Grabenstetter et al., incorporated herein by reference.

Other optional components useful in the present invention are pyrophosphate salts such as those described in U.S. 4,515,772, May 7, 1985 to Parran et al. incorporated herein by reference. Also useful are nonionic antimicrobials such as triclosan described in U.S. 4,894,220, January 16, 1990 to Nabi et al. Both patents are incorporated herein by reference.

Another agent which can be used in the present compositions is an alkali metal bicarbonate, such as sodium bicarbonate. These are stable items of commerce and can be used together with a peroxide compound in separate compartments such as disclosed in U.S. 4,849,213 and U.S. 4,528,180, both to Schaeffer, incorporated herein by reference in its entirety.

Other preferred compositions of the subject invention are controlled-release drug delivery systems for placement in the periodontal pocket. Such systems include, but are not limited to, the cellulose hollow fibers disclosed in U.S. Pat. No. 4,175,326, issued to Goodson on Nov. 27, 1979; the ethylcellulose films disclosed in U.S. Pat. No. 4,568,535 issued to Loesche on Feb. 4, 1986; the absorbable putty-like material disclosed in U.S. Pat. No. 4,568,536 issued to Kronenthal, Maftai and Levy on Feb. 4, 1986; the biodegradable microspheres and matrix disclosed in U.S. Pat. No. 4,685,883 issued to Jernberg on Aug. 11, 1987; the microparticle or microcapsule suspensions disclosed in U.S. Pat. No. 4,780,320 issued to Baker on Oct. 25, 1988; the polymeric devices disclosed in European Patent Application No. 0,140,766 of Goodson, published May 8, 1985; and the lactide/glycolide executions described in U.S. Patent No. 5,198,220, March 30, 1993 to Damani; these patents are incorporated herein by reference. Such controlled-release delivery systems generally include a solid matrix, usually of polymeric material, loaded with one or more active agents, the matrix entrapping stannous gluconate. Typically, the active agents diffuse from the solid material into the periodontal pocket over time.

Preferred controlled-release drug delivery systems comprise from about 0.001% to about 50%, more preferably from about 0.01% to about 25%, more preferably still from about 0.1% to about 15%, still more preferably from about 1% to about 10%, of stannous gluconate and a controlled-release carrier.

The pH of the present compositions and/or its pH in the mouth can be any pH which is safe for the mouth's hard and soft tissues. Such pH's are generally from

about 3 to about 10, preferably from about 5 to about 9.

METHOD OF MANUFACTURE

The carrier compositions used in the present invention can be made using methods which are common in the oral products area.

- 5 For example, toothpaste compositions may be prepared by mixing part of the humectant and water together and heating to 66°-71°C. The fluoride source, if present, is then added along with the sweetener, the opacifier and the flavor.

COMPOSITIONS OF USE

- 10 The present invention in its method aspect involves applying to the gingival and/or oral mucosal tissue safe and effective amounts of the compositions. Generally an amount of at least about 5 grams of a mouthwash and at least about 0.5 grams of a toothpaste or liquid dentifrice.

- 15 A preferred method of the subject invention involves the contact of a composition of the subject invention with oral cavity soft tissue for at least about 15 seconds, preferably from about 20 seconds to about 10 minutes, more preferably from about 30 seconds to about 60 seconds. The method often involves expectoration of most of the composition following such contact, preferably followed by rinsing, e.g., with water. The frequency of such contact is preferably from about once per week to about five times per day, more preferably from about thrice per week to about four times per day, more preferably still from about once per day to about thrice per day. The period of such treatment typically ranges from about one day to a lifetime. Generally, people may recognize that they will be exposed to a cold's virus and they then can use the products described herein either prior to the exposure, following exposure, or at the first signs of a cold.

- 25 The compositions used in the present method may also be used by the subject as a gargle. Additionally, subjects taking large doses of Vitamin C may obtain an enhanced colds benefit through the use of compositions described herein.

- 30 The following examples further describe and demonstrate preferred embodiments within the scope of the present invention. The examples are given solely for illustration and are not to be construed as limitations of this invention as many variations thereof are possible without departing from the spirit and scope thereof.

EXAMPLE I

Toothpastes

	<u>Weight %</u>	<u>Weight %</u>
35 Water	13.017	12.500
Sorbitol	45.425	44.552

	Glycerin	10.198	10.198
	Titanium Dioxide	0.525	0.525
	Silica	20.000	20.000
	Na Carboxymethyl Cellulose	1.050	1.050
5	Magnesium Aluminum Silicate	0.408	0.408
	Na Alkyl Sulfate (27.9% Solution)	4.000	4.000
	Na Zn Citrate		
	Na Saccharin	0.200	0.200
	Flavor	0.851	0.851
10	FD&C Blue #1 (1% Solution)	0.051	0.051
	Na Monofluoro Phosphate	0.243	-
	Na Hydroxide (50% Solution)	0.500	0.395
	pH	4.5	4.5

EXAMPLE II15 **Mouthrinses**

		<u>Weight %</u>	<u>Weight %</u>
	Na Zn Citrate		
	Glycerin	8.000	12.000
	Sorbitol (70% Aqueous Solution)	-	-
20	Ethanol	10.000	10.000
	Polysorbate 80	0.300	0.300
	Sodium Saccharin	0.050	0.050
	Flavor	0.150	0.150
	Sodium Hydroxide	0.020	0.020
25	Benzoic Acid	0.050	0.050
	FD&C Blue #1 (1% Solution)	0.020	0.020
	Sodium Monofluoro Phosphate	0.183	-
	Water	80.187	77.850

EXAMPLE III30 **Topical Gels**

		<u>Weight %</u>	<u>Weight %</u>
	Na Zn Citrate		
	Glycerin	91.896	70.000
	Sorbitol (70% Solution)	-	21.765
35	Sodium Carboxymethyl Cellulose	0.600	0.800
	Hydroxyethyl Cellulose	-	-
	Flavor	1.000	1.000

Sodium Saccharin	0.200	0.200
Sodium Alkyl Sulfate (27.9%)	2.000	2.000
Sodium Monofluoro Phosphate	0.760	-

EXAMPLE IVMouthrinse Tablets

5	Na Zn Citrate		
	Flavor	0.150g	0.150g
	Sodium Saccharin	0.050g	0.200g
	Mannitol	0.773g	-
10	Sodium Carboxymethyl Cellulose	0.050g	-
	Sodium Benzoate	0.030g	0.025g
	Citric Acid	-	0.200g
	Sodium Carbonate	-	0.100g
	Sodium Bicarbonate	-	0.200g
15	Glycine	-	0.050g
	Sodium Monofluoro Phosphate	<u>0.183g</u>	<u>-</u>
		2.255g	2.144g
		Dissolve	Dissolve
		in 97.745g	in 97.856g
20		water	water

WHAT IS CLAIMED IS:

1. A method of reducing the incidence of colds and similar maladies, such as flu, in animals susceptible to colds comprising applying to the gingival and/or oral mucosal tissue of said animal an effective amount of a composition containing an effective amount of an alkali metal or ammonium zinc citrate.
2. A method according to Claim 1 wherein said composition is in the form of a toothpaste.
3. A method according to Claim 1 wherein said composition is in the form of a mouthrinse.
4. A method according to Claim 1 wherein said composition is in the form of a site specific delivery system.
5. A method according to Claim 1 wherein the concentration of an alkali metal or ammonium zinc citrate is from about 0.1% to about 11%.
6. A method according to Claim 2 wherein said toothpaste contains a silica abrasive.
7. A method according to Claim 6 wherein the zinc salt is sodium zinc citrate.
8. A method according to either of Claims 6 or 7 which in addition contains a fluoride ion source.
9. A method according to any of Claims 6-8 which in addition contains an agent selected from the group consisting of surfactants, humectants, sweetening agents and mixtures thereof.
10. A method according to any of Claims 6-9 wherein the humectant is selected from the group consisting of sorbitol, glycerin, xylitol and mixtures thereof.

INTERNATIONAL SEARCH REPORT

Internat. Application No

PCT/US 97/19153

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/315 //A61K7/24,A61K7/16

According to International Patent Classification (IPC) or to both national classification and IPO

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 409 905 A (G.E. EBY) 25 April 1995 see the whole document ---	1-10
A	US 4 325 939 A (N. B. SHAH) 20 April 1982 cited in the application see the whole document ---	1-10
A	US 4 289 754 A (D. J. DABHAR) 15 September 1981 cited in the application see the whole document, especially column 2 lines 31-53 and columns 3-6 --- -/-	1-3,5, 7-10

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

20 February 1998

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

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Internat'l Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Week 8931 Derwent Publications Ltd., London, GB; AN 89-220777 XP002056504 & AU 88266 77 A (CARANTINOS S.) , 8 June 1989 see abstract</p>	1
A	<p>--- MARTIN : "pH as a variable in free zinc ion concentration from zinc-containing lozenges" ANTIMICROB. AGENTS CHEMOTHER., vol. 32, April 1988, pages 608-609, XP002056500 see the whole document</p>	1
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A	<p>--- EBY: "Linearity in dose-response from Zinc lozenges in the treatment of common colds" J. PHARM. TECHNOL. (USA), vol. 11, no. 3, 1995, pages 110-112, XP002056502 see the whole document, especially page 116 left column</p>	1
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/19153

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-10
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.

PCT/US 97/19153

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